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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/782,899	02/23/2004	Minoru Fujimori	12381-002-999	5937
20583	7590	08/21/2008	EXAMINER	
JONES DAY 222 EAST 41ST ST NEW YORK, NY 10017			LONG, SCOTT	
			ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/782,899	Applicant(s) FUJIMORI ET AL.
	Examiner SCOTT LONG	Art Unit 1633

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 23 May 2008.
 2a) This action is **FINAL**. 2b) This action is non-final.
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 47-72 is/are pending in the application.
 4a) Of the above claim(s) 65-72 is/are withdrawn from consideration.
 5) Claim(s) _____ is/are allowed.
 6) Claim(s) 47-52 and 58-64 is/are rejected.
 7) Claim(s) 53-57 is/are objected to.
 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

The examiner acknowledges receipt of Applicant's Remarks and Claim amendments, filed on 23 May 2008.

Claim Status

Claims 1-46 are cancelled. Claims 47-72 are newly submitted. Claims 65-72 are withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Claims 47-64 are under current examination.

Priority

This application claims benefit as a Continuation of U.S. Application No. 09/816,391 filed 26 March 2001 (abandoned). The instant application also claims benefit from foreign application JAPAN 2000-287688 filed 12 September 2000. The application has been granted the benefit date, 26 March 2001, from U.S. application 09/816,391 because no English translation of foreign application JAPAN 2000-287688 has been submitted.

RESPONSE TO ARGUMENTS

Claim Rejections - 35 USC § 112

The rejection of claims 28 and 30-46 rejected under 35 USC 112, first paragraph (written description), is withdrawn in response to Applicant's amendment or arguments. The applicant has cancelled claims 28 and 30-46; therefore, the pending rejections were made moot.

Claim Rejections - 35 USC § 103

The rejection of claims 28 and 30-46 under 35 U.S.C. 103(a) as being unpatentable over Yazawa et al. (Proceedings of the American Association for Cancer Research Annual Meeting, Vol. 40, pp. 88, 1999) in view of Brown et al. (US applic. 2003/0103952) and further in view of Goshima et al. (Biochimie, 1990. vol.72: 207-214) and further in view of Natori et al. (Biochimie. Volume 70, Issue 12, December 1988, Pages 1765-1774) is withdrawn in response to Applicant's amendment or arguments. The applicant has cancelled claims 28 and 30-46; therefore, the pending rejections were made moot.

NEW GROUNDS OF REJECTION

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 52 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 52 recites “wherein the HU protein promoter and terminator are the HU promoter and terminator depicted in SEQ ID NO:1”. SEQ ID NO:1 is a sequence which shows both a polynucleotide sequence and polypeptide sequence. A skilled artisan would clearly know which portion of the polynucleotide sequence corresponds with a coding sequence, but since no indication is provided for the promoter and terminator portions of SEQ ID NO:1, the examiner believes the current claim language to be indefinite in regard to “depicting” such promoter and terminator sequences in SEQ ID NO:1. Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or non-obviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 47-51 and 58-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yazawa et al. (Proceedings of the American Association for Cancer Research Annual Meeting, Vol. 40, pp. 88, 1999) in view of Brown et al. (US applic. 2003/0103952) and further in view of Goshima et al. (Biochimie, 1990. vol.72: 207-214) and further in view of Claret et al. (J. Mol. Biol. 1997; 273: 93-104).

Yazawa teaches using *Bifidobacterium longum* as a gene delivery vector for treating cancer in a buffer or solution, (that is, a pharmaceutical preparation). However, Yazawa does not specifically teach introducing a DNA coding for a protein having an

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activity of converting a precursor of an anti-tumor substance into the anti-tumor substance into a tumor using *Bifidobacterium longum*.

However, at the time the invention was made, introducing a DNA coding for a protein having an activity of converting a precursor of an anti-tumor substance into the anti-tumor substance into a tumor using a genetically modified bacterium was well known to one of ordinary skill in the art as exemplified by Brown (columns 1-26). Brown teaches using a genetically modified bacterium to deliver an enzyme to the hypoxic/necrotic environment of a tumor and systemically administering a pro-drug, which is converted at the site of the tumor to the toxic agent by the enzyme (columns 25-26). The enzyme/prodrug combination can be selected from following: nitroreductase/CB1954; cytosine deaminase/5-fluorocytosine; beta glucuronidase/ glucuronidated anticancer drugs (columns 5-6).

Neither Yazawa et al. nor Brown et al. teach utilizing the strong promoter, histone-like DNA binding protein (HU) promoter, in recombinant *Bifidobacterium longum* in order to express anti-tumor genes.

However, the HU promoter was known as in the art as a promoter which highly expresses HU protein in *E. coli* during logarithmic growth phase (Claret et al.). It was further known in the art that the HU was highly conserved during evolution between *E.coli* and *Bifidobacterium longum* (Goshima et al.). However, utilizing the strong promoter, histone-like DNA binding protein (HU) promoter, in recombinant *Bifidobacterium longum* in order to express anti-tumor genes was not performed by any

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other researchers at the time of the filing. The examiner still believes that it is obvious to use *Bifidobacterium longum* as a vehicle for delivery of cancer therapeutics.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to modify the teaching of Yazawa taken with Brown, Goshima and Claret, namely to use a genetically modified *Bifidobacterium longum* comprising a nucleic acid sequence encoding a protein having an activity of converting a precursor of an anti-tumor substance into the anti-tumor substance in a method to treat tumor tissues under anaerobic conditions and further using the HU promoter to express the anti-tumor substances.

One of ordinary skill in the art would have been motivated to introduce the DNA encoding a protein having an activity of converting a precursor of an anti-tumor substance into the anti-tumor substance into tumor tissues under anaerobic conditions using the genetically modified bacterium because the bacterium is a nonpathogenic anaerobic bacterium, which can selectively localize to solid tumors in an individual after systemic application and pro-drug cancer therapy was well known to one of ordinary skill in the art for treating tumor tissue.

In addition, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to modify the teaching of Yazawa taken with Brown, namely to use any enzyme/prodrug combination in the method to treat tumor tissues under anaerobic conditions. One of ordinary skill in the art would have been motivated, as a matter of designer's choice, to use an enzyme/prodrug combination selected from following: nitroreductase/CB1954; cytosine deaminase/5-fluorocytosine;

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beta-glucuronidase/glucuronidated anticancer drugs because the enzyme/prodrug combinations were well known to one of ordinary skill in the art for treating hypoxic tumor tissue.

In addition, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Yazawa taken with Brown and Goshima and Claret, namely to use an expression vector that has a HU promoter and terminator that function in a Bifidobacterium. Furthermore, one of ordinary skill in the art would have been motivated to use the HU promoter in *B. longum* to express anticancer genes because Goshima, in particular, suggest *B. longum* could be used in the medical sciences.

One of ordinary skill in the art would have been motivated to use a histone-like binding protein promoter and terminator of Bifidobacterium because one of ordinary skill in the art understands that a promoter and a terminator are required for the vector to express the protein of interest. Furthermore, having a promoter which expresses an important protein such as those interacting with histones could provide high levels of expression of the anti-tumor substance.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Allowable Subject Matter

Claims 53-57 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

No claims allowed.

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Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SDL/ Scott Long
Patent Examiner, Art Unit 1633

/Janet L. Epps-Ford/
Primary Examiner, Art Unit 1633